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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,158	GENARD, SYLVIE	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/11/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,15-25 and 27-46* is/are pending in the application.

4a) Of the above claim(s) *20-25 and 29-45* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *1-11,15-19,27,28 and 46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 March 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response and amendment are acknowledged, following the RCE are acknowledged.

Election/Restrictions

As indicated previously, Applicant's election of Group I in the reply filed on 6/26/06 (Original Restriction requirement under former Examiner Shirali) is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). A second supplemental Restriction requirement was sent by this Examiner on 9/25/06, including an election of species. Thereafter, on 12/12/06, via Interview, the Examiner rejoined Group II with Group I, such that this is now the elected invention (collectively now Group I, claims 1-19, 27-28, 32-38, and 45). Additionally, a species election as to a method of making a complete identified compound species of Formula I was required, to which Applicant elected the compound shown on page 3 of the restriction response of 12/18/06. Claims 1-19 and 27-28 read on the elected species.

Claims 20-26 and 29-45 are withdrawn from consideration as being withdrawn from non-elected species (claims 32-38 and 45) or invention (claims 20-26 and 29-44). Claims 1-19 and 27-28 are examined on the merits as drawn to the elected Group I and species.

The Invention

As indicated previously, paragraph 250 of Applicant's Published Application describes the method of preparing the presently elected/claimed invention, namely: "Synthesis of the KPV Tripeptide Diacetyl Derivate under the form of Various Salts", in its diamide form.

It is noted that applicant has amended claim 12 into base claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11, 15-19, 27-28, and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eberle et al. (HELVETICA CHIMICA ACTA (1975), 58(7), 2106-29 (cited in Applicant's IDS 1/23/04), in view of Ferreiri (US 5580855), Lipton et al. (US 5,028,592) and Kauvar et al. (US 5,786,336).

Eberle et al. teach, as Applicant indicated in the following para's:

[0009] To the Applicant's knowledge, [no? sp?] one single publication discloses the solution synthesis of diamide compounds of the KPV tripeptide, the only exemplified compound being Ac-Lys-Pro-Val-NH.sub.2 (Eberle et al., 1975).

[0052] It has been shown that **an appropriate selection of the protective groups, the reagents to be used and the reaction sequence makes it possible to increase the yield**,

in a solution synthesis, from 33% (Eberle et al., 1975) to more than 70% in the case of Ac-Lys-Pro-Val-NH2.

It is noted that Applicant, like the new reference, Ferreira et al., both cite A.N. Eberle works in this art of modifying KPV tripeptide protective groups in order to, as Applicant noted on page 17 of his last response and as recited in para 52 of the specification (and in the IDS of 1/23/04), "possibly" increase yields. [NOTE: As Applicant noted on page 17 of the response with the RCE, Applicant did not per se find any increased yields via his process, but merely noted that Eberle et al. teach that it is possible.]

TWO OTHER KPV SYNTHESIZING EXAMPLES

Ferreira et al. teach that the tripeptide Lys-Pro-Val (KPV) was synthesised and purified in accordance with the procedure described in Example 1 (Example 4, col. 6, bottom); (evidencing a scaffold that ironically used a diamine cross-linker), wherein "[t]he tripeptide Lys-Pro-Thr was synthesised using the Fmoc-polyamide method of solid-phase peptide synthesis (Dryland and Sheppard, Peptide Synthesis 8 "A system for solid phase synthesis under low pressure continuous flow conditions" J. Chem. Soc. Perkin. Trans. 1, 125, 1986). The solid phase support was a polydimethylacrylamide polymer constituted from the three monomers dimethylacrylamide (backbone monomer), *bis-acryloyl-ethylene diamine* (cross-linker) and acryloylsarcosamine methyl ester, (functionalising agent). The peptide to resin clearable linked agent used was the acid labile 4-hydroxymethyl-phenoxyacetic acid derivative" (Example 1, column 5). It is also noted that Ferreira et al. also recite a later

reference to A. N. Eberle, A. N. (ed) "The Melanotropins, chemistry . . . ", Karger Press, 1988, pp. 336-337 and 346-348.

Lipton et al. teaches a method of making diacetyl KPV tripeptides and salts thereof (one of a number of patents Lipton et al. have since the late 80's and into the '90's on such KPV analogs and methods of making the same), for the treatment of various cellular disorders (e.g. inflammation) (see entire document, especially abstract; col. 8, line 55+). Lipton et al. was not found to expressly teach the synthesis of a KPV tripeptide "diamide" per se. Lipton et al. teach at col's 6-7:

It is believed that many changes may be made in the amino acid sequence of the peptides of the present invention and still obtain a protein which exhibits a biologically functional equivalent pharmacologic activity. For example, it has been found by Kyte et al. (1982), J. Mol. Biol., 157:105, that certain amino acids may be substitute for other amino acids having a similar hydropathic index, and still retain the biologic activity of the protein. As displayed in the table below, amino acids are assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics. It is believed that the relative hydropathic character of the amino acid determines the secondary structure of the resultant protein, which in turn defines the interaction of the protein with its receptor.

In the case of the present peptides, it is believed that biological functional equivalents may be obtained by substitution of amino acids having similar hydropathic values. As used herein, a biological functional equivalent is defined as a protein that is functionally equivalent in terms of biological functional equivalent is defined as a protein that is functionally equivalent in terms of biological activity. Thus, for example, isoleucine of leucine have a hydropathic index of +4.5 and +3.8, respectively, can be substituted for valine (+4.2), and still obtain a protein having like biological activity. Alternatively, at the other end of the scale, lysine (-3.9) can be substituted with arginine (-4.5), and so on. In general, it is believed that amino acids can be successfully substituted where such amino acid has a hydropathic score of within about +/-1 hydropathic index unit of the replaced amino acid.

The following examples illustrate experiments conducted by the present inventor to illustrate the production of the preferred tripeptide, as well as various "protected" species, and use of the tripeptide in various accepted in vivo assays which demonstrate its activity. It will be appreciated that these examples are illustrative only and variations may be made in light thereof and in light of the level of skill in the art. Thus, for example, where peptides having different sequences, or longer or shorter peptidyl length, are desired, it will be apparent to those of skill in the art that the procedures generally as set forth below may be employed. Accordingly, where the sequence arg-pro-val is desired (a biologically functional equivalent of lys-pro-val), it will be apparent that dibenzyloxycarbonyl-confugated arginine ("Z-arg") should be employed in the

place of "Z-arg") . Moreover, where, for example, gly-lys-pro-val is desired, it will be apparent that "Z-gly" should be employed as the starting reagent and synthetic steps employed as set forth to sequatically add the lys, pro and val residues, respectively. These and all other modifications to achieve the various peptides are well known and will be apparent to those of skill.

A DIAMIDE TRIPEPTIDE SYNTHESIZING EXAMPLE

Kauvar et al., as cited previously, teach the synthesis of tripeptides as well (not KPV per se) and **as to the diamide form of tripeptides specifically**; "It has further been found that in order to exert intracellular effects, the compounds of the invention are preferably supplied as the diamides or diesters or hybrids thereof" (col. 2, lines 37-40).

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to synthesize the well known KPV tripeptide in it's diamide form in Eberle et al., because Eberle advantageously teach that "[i]t has been shown that **an appropriate selection of the protective groups, the reagents to be used and the reaction sequence makes it possible to increase the yield**, in a solution synthesis, from 33% (Eberle et al., 1975) to more than 70% in the case of Ac-Lys-Pro-Val-NH2"; while at least two other examples teach other routine optimizations for synthesizing KPV, namely Ferreira et al. (also citing a later A.N. Eberle et al. reference to KPV synthesizing) and Lipton et al. advantageously teaching the diacetyl KPV tripeptide synthesis methods; in view of the peptide artisans understanding that the diamine/diamide tripeptide synthesis in Kauvar et al. could be advantageously optimized and used for ANY tripeptide, depending on the desired end results - particularly if greater yields were being considered, in line with Eberle et al.'s indication that modifications to the KPV synthesis technique could increase yields 33->70%.

Furthermore, in view of Kauver, who teach that in the peptide arts it was known that the diamide form of tripeptide synthesis allows for such tripeptides to optimally exert intracellular effects and one of ordinary skill in the peptide arts would have been motivated to modify the KPV tripeptide synthesis method of Eberle et al. to incorporate the diamide form, to allow greater intracellular effects by the KPV tripeptide in the methods of use, for instance like the KPV tripeptide in intracellular disorders (e.g. inflammation) described by Lipton et al.

[As noted previously, the addition of new claim 46 to negatively claim out that no final purification step need to applied, is simply deemed a matter of routine optimization depending on the degree of purity desired. One of skill in the art would not look to Lipton et al. and believe that a final purification step must be instituted in order to arrive at the same KPV compound created in the present method.]

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MA, 1/19/2008

/Maury Audet/
Examiner, Art Unit 1654